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Central control of visceral pain and urinary tract function

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Abstract

Afferent input from A δ and C-fibres innervating the urinary bladder are processed differently by the brain, and have different roles in signaling bladder sensation. A δ fibres that signal bladder filling activate a spino-bulbo-spinal loop, which relays in the midbrain periaqueductal grey (PAG) and pontine micturition centre (PMC). The excitability of this circuitry is regulated by tonic GABAergic inhibitory processes. In humans and socialized animals micturition is normally under volitional control and influenced by a host of psychosocial factors. Higher nervous decision-making in a social context to 'go now' or 'do not go' probably resides in frontal cortical areas, which act as a central control switch for micturition. Exposure to psychosocial stress can have profoundly disruptive influence on the process and lead to maladaptive changes in the bladder. During sleeping the voiding reflex threshold appears to be reset to a higher level to promote urinary continence.

Under physiological conditions C-fibre bladder afferents are normally silent but are activated in inflammatory bladder states and by intense distending pressure.

Following prolonged stimulation visceral nociceptors sensitise, leading to a lowered threshold and heightened sensitivity. In addition, sensitization may occur within the central pain processing circuitry, which outlasts the original nociceptive insult.

Visceral nociception may also be influenced by genetic and environmental influences.

A period of chronic stress can produce increased sensitivity to visceral pain that lasts for months. Adverse early life events can produce even longer lasting epigenetic changes, which increase the individual's susceptibility to developing visceral pain states in adulthood.

Keywords: micturition, central nervous control, visceral pain, bladder

Despite its autonomic nature, the bladder is by no means an autonomous structure; normal bladder filling and emptying does not occur without the involvement of the central nervous system. Although there is some organisation at sacral spinal level (see ***** this issue), following spinal injury bladder dysynergia is a serious problem that impacts significantly on the individual's quality of life. Even following spinal injury at supra sacral levels voiding is not normal, implying a critical dependence on the brain.

The sophisticated nature of the control over micturition is perhaps under-appreciated.

In the newborn, urinary voiding is a reflex process driven by the fullness of the bladder, but as the individual matures voiding becomes a volitional process. In addition, the threshold for micturition is not fixed. In humans and many socialised animals, social mores dictate that voiding is appropriate only under certain circumstances. Humans may suppress voiding for relatively long periods of time despite fullness of the bladder, until the relevant social conditions are met. House training of domestic pets instills a similar degree of control. When a suitable opportunity presents itself, humans can empty a partly filled bladder, in order to maximize the interval before the next void. If needed, there is also the facility to halt the micturition process mid-stream i.e. switch on or off at will.

Volitional control is also exhibited in many undomesticated but socialised species.

For example, specific 'toilet' areas can be identified within the cages of laboratory rats and mice. Controlled partial voiding in order to release small quantities of urine for scent marking is another example of voiding behaviour that requires very precise

volitional control of the autonomic outflows. In addition, micturition does not normally occur during sleep. The high level of decision-making and precise motor control over the micturition reflex has lead to the concept of “cognitive voiding” (Fig 1; Gillespie, 2013), which implies significant forebrain involvement.

The act of voiding requires a co-ordinated sequence of events, which includes contraction of the detrusor and relaxation of the external urethral sphincter muscles, usually accompanied by various postural adjustments. In some species (e.g. rats and dogs), the sphincter muscle undergoes a period of rhythmic contraction and relaxation during voids, which is thought to increase the velocity of flow in the urethra and enable spurting of urine for scent marking (d’Amico et al, 2011; Conte et al., 1991; Maggi et al, 1986; Matsuura et al., 1998, 2000). These co-ordinated events require the functional integrity of the spino-midbrain-spinal loop and are absent after spinal transection (d’Amico et al, 2011).

Basic spinal-midbrain-spinal pathway for micturition

The spino-midbrain-spinal circuit, which relays in the midbrain periaqueductal grey matter (PAG) and pons (pontine micturition centre or Barrington’s nucleus) has been the subject of a number of comprehensive reviews in recent years (Fowler et al., 2008; Holstege 2010; Drake et al., 2010; de Groat and Wickens, 2013). It will therefore be considered only briefly here, for completeness.

Filling of the bladder is detected by stretch-sensitive afferent nerves in the bladder wall. Among distension-sensitive bladder afferents, low threshold myelinated A-delta fibers acting as ‘in series’ tension receptors (Iggo, 1955) are considered to be mainly

involved in control of micturition and several functional classes of distension-sensitive afferents have been identified (Zagorodnyuk et al., 2007). In contrast, high threshold afferents (intravesical pressure >20 mmHg) have been associated with the generation of painful sensations (de Groat, 1997). Afferent information on filling status is relayed to the brain by a group of neurons in the lateral funiculus of the upper sacral cord, just lateral to the dorsal horn. Anatomical studies in cats indicate that cells in this region project rostrally to terminate bilaterally in the central part of the PAG (Vanderhorst et al., 1996) although in the rat, electrophysiological and anatomical evidence favours dorsal and ventrolateral targets for the projection (Ding et al., 1997; Duong et al., 1999; Marson, 1997; Mitsui et al., 2003). In rats there is also a direct projection from the sacral cord to the PMC (Ding et al., 2007), which if activated by bladder distension, could potentially short-circuit the PAG. However, this direct pathway does not appear to play a significant role in initiating voiding, at least under urethane anaesthesia, because lesions or pharmacological inhibition of synaptic transmission through the PAG prevent normal micturition from taking place (Matsumoto et al., 2004; Matsuura et al., 1998; 2000; Stone et al., 2011). Comparable information from humans is limited but even so, urinary retention was reported to accompany the development of a space occupying lesion in the PAG (Yaguchi et al., 2004) whilst in multiple sclerosis sufferers retention or incontinence have been associated with the presence of demyelinating lesions in the midbrain and pons close to the periaqueductal grey matter and pontine micturition centre (Charil et al., 2003).

Efferents from the PAG project to the pontine micturition centre (PMC, also known as Barrington's nucleus), which in turn sends projections directly to preganglionic parasympathetic neurones in the sacral cord that regulate the activity of motor

neurons innervating the detrusor and urethral sphincter muscles (Holstege, 2010; Fowler et al., 2008; Drake et al., 2010; deGroat and Wickens, 2013 for reviews). In cats, but not in rats, more laterally in the pons lies the pontine storage centre or ‘L-region’ where electrical stimulation induces contraction of the external urethral sphincter (EUS) and relaxation of the bladder (Holstege et al., 1986). Anatomical connections between this region, the PMC and the PAG have yet to be demonstrated however.

A central switch for micturition that requires higher nervous decision-making in a social context.

The spino-midbrain-spinal loop is undoubtedly the foundation of micturition control. However, this circuit does not function simply as a relay whereby a set level of afferent input arising from the bladder triggers a void. Integral to the concept of cognitive voiding (see above) is that cues from the external as well as internal environment control a neural “switch” for voiding. The nature of control of the switch is still a matter of debate. In one scenario the switch is “off” during the resting (filling) state but can be flipped to the “on” position to initiate a void. An alternative scenario would be a switch that is normally “on” and tonically inhibiting the micturition circuitry but is switched to the “off” position to permit voiding to occur. In practice, both mechanisms might be present.

The location of the “switch” is also a matter of debate. Beckel and Holstege (2014) have suggested that a neural switch that turns on voiding resides in a region of the dorsolateral pons they term the pelvic organ stimulating centre (POSC, corresponding to the pontine micturition centre), but the hand that “throws” the switch lies in the

PAG. This is an attractive proposition since the PAG cannot evoke voiding without engaging the PMC and the PMC and, with the exception of rats, does not receive direct information from the bladder (see de Groat and Wickens 2013 for a recent discussion of this point). Neurones in both the PMC and PAG display changes in firing rate that correlate with changes in vesicular pressure during isovolumetric contractions evoked by distending the bladder with the outlet ligated (e.g. Liu et al., 2004; Sakakibara et al., 2002; Sugaya et al., 2003; Tanaka et al., 2003). Based on the properties of such cells deGroat and Wickens (2013) have proposed a simple computer model of the micturition circuit. It will now be important to test their model with data obtained from cells recorded during physiological micturition i.e. when actual voiding takes place.

The location of the micturition on-off switch is of paramount importance as it could be key to understanding certain forms of urge incontinence. Studies in animal models are fleshing out the physiological and anatomical details of the basic voiding circuitry. However the question of switching may best be answered by recording activity during voiding in the conscious state. As the resolution of brain imaging technology improves, such studies are becoming feasible in animals. An fMRI study in sedated rabbits reported activation in both PAG and PMC after filling the bladder to 70% capacity, but without voiding (Xiang et al., 2010). In a study in rats under urethane anaesthesia the PAG but not the PMC, was activated during filling. However when bladder volume reached the voiding threshold, the intensity of the PAG signal increased further and activation was also detected in the PMC (Tai et al., 2009). The results of this elegant study are consistent with the PAG monitoring bladder volume during the filling phase and then ‘switching on’ the PMC to initiate a void.

Forebrain control of bladder function

Whilst the finer details of the micturition switch remain to be worked out, another important question to consider is what determines the status of the switch? For many years investigations into the control of voiding at forebrain level were restricted by the use of anaesthetized animal models in which synaptic transmission in forebrain structures is necessarily depressed. However, the field opened up with the advent of modern high resolution imaging techniques, which could be applied to conscious human subjects. In 2010 a meta-analysis of the data gathered from the first decade of brain imaging of micturition in humans enabled Fowler and Griffiths (2010) to propose a working model of lower urinary tract control by higher centres. In essence, they proposed that during storage, information on bladder status carried by spinal afferents is relayed directly to the midbrain periaqueductal gray (PAG) and also activates the hypothalamus, thalamus, dorsal anterior cingulate cortex, right insula and lateral prefrontal cortex. In the prefrontal cortex the decision to void or not may be made. If the decision is to “go” the medial prefrontal cortex, which during storage is tonically inhibiting transmission through the PAG and the downstream pontine micturition centre is disinhibited, thereby allowing a void to proceed. At the same time the hypothalamus may also provide a “safe” signal to the PAG. In their more recent comprehensive review of forebrain influences Griffiths and Fowler (2013) extended their original model and proposed in addition, the existence of a back-up continence mechanism which in cases of extreme urgency, can bypass the brainstem switch to promote continence by activating a pathway from the anterior cingulate region to the pontine storage centre (Fig 2).

The results from basic studies in animal models lend support to the concept of top down gating of the ponto-medullary micturition circuit by the pre-frontal area (Griffiths and Fowler, 2013) via a neural micturition "switch" in the PAG, which permits the downstream PMC to initiate a void. In rats the critical synaptic relays in the micturition circuit lie within the ventrolateral PAG, the region that sends projections to the PMC (Kuipers et al., 2006). These regions are normally subject to a tonic GABAergic influence (Stone et al., 2011). When voiding takes place a decrease in concentration of extracellular GABA in the PAG occurs (Kitta et al., 2008), presumably reflecting a lift of the tonic inhibition. This would be expected to increase the excitability of the PAG, and thereby stimulate the efferent projection to the PMC to trigger voiding, in line with the results obtained during imaging by Tai et al. (2009) (see above).

The source of the inhibitory GABAergic tone in the PAG has not yet been established. However, in rats and in primates the prefrontal cortex sends dense projections to the ventrolateral PAG (An et al., 1998; Floyd et al., 2000), which might be a source of the tonic inhibition during filling. The inhibitory nature of the input to the PAG from the medial frontal lobe is suggested by the observation that stimulation in this area prolonged the interval between bladder contractions in conscious rats that were undergoing continuous cystometry (Nishijima et al., 2012). Whether the inhibitory projection is direct or mediated by activation of local GABAergic interneurons in the PAG is not known.

In humans the involvement of the medial prefrontal cortex (PFC) in decision-making, based on the social situation, is well established (Adolphs, 1999). More recently,

sophisticated multilevel path modelling approaches to imaging have shown that social evaluative threat (SET) can influence functional connections between the frontal cortical regions, the PAG and autonomic output (Wager et al., 2009). In the context of micturition, when mental appraisals are translated into an adaptive physiological response, SET might be experienced as the potential humiliating consequences of failing to maintain continence in a given social situation.

There are many other aspects of micturition control in which the forebrain is undoubtedly involved. For example, the sense of urgency is not always directly related to bladder volume and indeed, appears to be remarkably plastic. It is a common experience that the need to void imminently can be subsumed at least temporarily if the individual is distracted and attention is diverted elsewhere. On the other hand a sense of urgency can suddenly and dramatically increase on the final approach to home - the “latch key” phenomenon. Paruresis, as exemplified by the inability to urinate in public toilets or in other people’s homes is another example of transient dysfunction of the bladder control system. Little is known about the central nervous basis of these effects, yet they are an integral part of daily life in humans and may be relevant to understanding disorders of bladder control.

What is well established from work in animal models, is that exposure to psychosocial stress exerts a powerful influence on bladder function. In rats 30min of daily exposure to water avoidance stress for 7 days is sufficient to promote urinary retention and abnormal urodynamics, which resemble those produced by partial bladder outlet obstruction (pBOO) (Wood et al, 2013). Mice too showed a similar stress-induced urinary retention and increased bladder mass (Chang et al, 2009).

1 Activation of CRF-containing neurons within Barrington's nucleus (pontine
2 micturition centre) appears to be integral to inducing this effect. These neurones send
3
4 projections to the spinal cord (Valentino et al, 1996) where they may produce
5
6 inhibitory effects. Intrathecal application of CRF increased bladder capacity and
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8 micturition volume in awake rats (Pavcovich and Valentino, 1995; Kiddo et al, 2006).
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10 However, these findings are equivocal since others have reported that CRF facilitated
11
12 micturition (Klausner et al, 2005).
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19 Interestingly pBOO induced experimentally in the absence of stress has been shown
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21 to increase expression of CRF in Barrington's nucleus. Thus a positive feedback loop
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23 could be activated whereby once exposure to psychosocial stress produces voiding
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25 dysfunctions and bladder pathology via activation of the CRF pathway, signals from
26
27 the dysfunctional viscera activate components of the basic micturition circuit to
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29 produce further neurobehavioral effects that are co-morbid with visceral pathology
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31 (Valentino et al, 2011). This vicious circle of events could give rise to long-lasting
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33 bladder dysfunction.
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41 Central regulation of bladder function during sleep

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44 Another challenge for the micturition control system is the sleep state. Humans
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46 require several hours of uninterrupted sleep daily in order to thrive. Micturition
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48 typically does not occur during the sleep period. This can be attributed in part to
49
50 reduced urine production as a consequence of the absence of fluid intake, combined
51
52 with the nocturnal increase in secretion of antidiuretic hormone. An endogenous
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54 circadian variation of bladder compliance has also been demonstrated. Bladder
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56 capacity increases during the sleep period due to functional changes in gap junctions
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1 in bladder smooth muscle cells that are associated with oscillating expression of
2 connexin43 (Negoro et al., 2012; 2013).
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7 The activity of brain circuitry controlling filling and voiding may also be reset during
8 sleep. In rats the micturition threshold increases during sleep (Kiddoo et al, 2006).
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10 Whether this is due to a centrally-mediated increase in descending tonic inhibitory
11 control on sensory input from the bladder at spinal levels which raises the threshold
12 for micturition during sleep and/or whether the threshold of the central voiding
13 circuitry is re-set to a higher level during sleep is not clear. A dynamic centrally-
14 mediated feed forward afferent control system has been identified, which increases
15 bladder compliance during filling (Smith et al., 2012), but it is not known whether the
16 activity of this system changes during sleep. However, in favour of this idea, we
17 found that during continuous cystometry carried out in rats under urethane
18 anaesthesia, micturition threshold increased and compliance decreased as the EEG
19 cycled from an activated to a de-activated sleep-like state (Fig 3). Urethane
20 anaesthesia is characterized by cyclical changes in EEG waveform that have been
21 proposed to model changing sleep states (Clement et al., 2008). Thus there may be a
22 centrally-mediated modulation of responsiveness to bladder filling, which changes in
23 different sleep states.
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48 Although decreased urine production and increased storage capacity of the bladder
49 reduce the likelihood of a need to void during the sleeping period, there are occasions
50 when micturition needs to take place. In conscious rats, EEG desynchronization
51 consistent with an arousal response (decrease in power in all frequencies) occurs just
52 prior to bladder pressure reaching the micturition threshold (Richenbacher et al, 2008;
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Valentino et al, 2011). This effect is associated with increased firing of neurones in locus coeruleus. It has been suggested that the increased arousal level facilitates disengagement from ongoing behavior and promotes a shift to elimination-related behaviors (Richenbacher et al, 2008). It is possible that activation of this system during sleep could serve as an “alarm” to induce arousal and alert the individual of the need to void, thereby preventing nocturnal enuresis.

Pain from the urinary tract

In the healthy individual there is little sensation from the bladder at low volumes. However, sensations are evoked in humans once bladder volume exceeds around 400ml and increases until a volume is reached which represents the individual’s “absolute need” to void (De Wachter et al., 2013). At the high end there may be acute discomfort coupled with a certain amount of anxiety but on the whole, micturition is not an overtly painful experience. However, in certain pathophysiological states, frank pain can arise from the urinary tract.

The encoding of noxious events by the viscera is mediated by several types of visceral nociceptor. These include high threshold receptors, silent nociceptors and high intensity coding receptors (Cervero and Jänig, 1992). A δ bladder afferents signal bladder status related to filling under normal conditions. However, the urothelium and the detrusor muscle are innervated by C-fibres as well. Bladder activated C-fibre activity was first demonstrated in a classic study by Iggo (1955) but whether these fibres would be recruited under physiological conditions was not clear.

It now appears that the C afferents of the lower urinary tract are normally quiescent

during filling but may become activated by extreme intravesicular pressure or in inflammatory bladder states (see Gonzales et al., 2014 for a recent review). In the ureters, which are a source of intense pain under pathophysiological conditions, the majority of afferents function as true nociceptors, remaining silent unless exposed to intense distension, although there exists a minority of low threshold fibres, which are sensitive to contractions of the ureter (Pedersen et al., 2010).

The brain processes input from the A δ and C fibres separately. Imaging studies of responsiveness to activation of nociceptive input from the bladder in humans are scarce. However intravesical administration of cold (4-8°C) saline, which preferentially activates C-fibres (Mehnert et al., 2011), caused a different supraspinal activation pattern, albeit with some overlap, compared to that evoked by activation of A δ fibres by bladder filling (Table I). The cold stimulus did not however evoke overt pain in the subjects; thus brain activation reflecting the emotional component of bladder pain may not be evident from this study. It should be noted that there are areas of overlap between brain regions activated by A δ and C-fibre afferents, e.g. in the PAG. However, it is likely that different functional sets of neurons in this structure are engaged to process information from A δ and C-fibre afferents.

Plasticity of visceral pain circuits – peripheral sensitisation

An interesting feature of the processing of visceral afferent input via C-fibres is the plasticity within the nociception circuitry. Although most basic research into the central processing of visceral sensation has focused on nociceptor input from the gut, evidence is now starting to accumulate, which suggests that these findings will generalize to the urinary tract (e.g. Pedersen et al., 2010; Gonzales et al., 2014).

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2 In the periphery persistent nociceptor stimulation due to intense pressure or the effects
3
4 of inflammatory mediators released at sites of injury and tissue damage, can sensitise
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6 nociceptors by reducing thresholds for activation and enhancing responsiveness. The
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8 combination of prolonged noxious stimulation and peripheral sensitisation of
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10 nociceptors induces a long lasting increase in excitability of the spinal cord and higher
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12 centre neurons, a phenomenon known as central sensitization (Latremliere and
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14 Woolf, 2009). This effect may persist even when there is no longer any afferent
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16 nociceptor input. Visceral pain states can also induce a change in gap junction
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18 coupling between cells in dorsal root ganglia (Huang et al., 2010) and activation of
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20 spinal microglia (Bradesi, 2010; Liu et al., 2012) which both serve to amplify activity
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22 in the nociceptive circuitry and maintain the pain state.
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31 Plasticity of visceral pain circuits – descending control systems

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33 In addition to the ‘bottom up’ mechanism of visceral nociception a ‘top down’
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35 modulation of afferent input from incoming signals occurs, which is mediated by
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37 activation of descending control systems from the brain. The descending modulation
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39 from cortical and limbic structures is a dynamic system. Emotional states such as
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41 stress, fear and anxiety exert potent, but complex, modulatory influences that can
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43 either suppress pain (stress-induced analgesia) or exacerbate painful states (stress-
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45 induced hyperalgesia; SIH) depending on the nature, duration and intensity of the
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47 stressor. This is exemplified in extreme conditions such as during a life threatening
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49 physical conflict, when pain may be completely suppressed. On the other hand, and
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51 perhaps more relevant to the clinical situation, milder stressors can exacerbate pain
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53 states. At the core of these effects is the modulation by cortical and subcortical
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structures of activity in a pathway from the PAG, which via relays in the ventromedial medulla, and modulates sensory transmission at the spinal level (Olango and Finn, 2014 for a recent review). Descending projections from the PAG also control bladder voiding (see above). However, these neurons are almost certainly functionally distinct from the pain modulatory circuit, although interactions may occur, particularly in bladder pain states.

Epigenetic and environmental influences on visceral sensitivity

Genetic and environmental influences on visceral hypersensitivity in humans are now well established. Traumatic early life events in particular, can produce long-term effects on the brain circuitry involved in visceral pain processing. There is much evidence for an association between abuse, particularly sexual abuse in childhood, and strong and persistent effects on gastrointestinal health and visceral pain in adulthood (Leserman and Drossman, 2008 for a review). The neuronal basis for such effects is under investigation. Women suffering from irritable bowel syndrome, who had a history of sexual or physical abuse, showed increased sensitivity to visceral pain (rectal distension) compared to non-abused patients, which correlated with a higher level of activation in the anterior and posterior cingulate cortices (Ringel et al., 2008). At the same time the level of activation in the supragenual cingulate, a region implicated in pain inhibition and arousal, was reduced (Ringel et al., 2008).

The development of animal models has started to shed further light of the underlying neuronal processes. To date most studies have focused on gastrointestinal disorders (Maloney et al, 2015) but as data becomes available on bladder sensitivity, it seems likely that similar findings will be made. As in humans, early life stress in rats has

1 been shown to produce a significant impact on visceral sensitivity in adulthood.
2 Maternal separation in early life is an especially powerful force, which increases
3 susceptibility to stress-induced visceral hypersensitivity, as shown by responsiveness
4 to colonic distension (Coutinho et al, 2002). Moreover, this effect could be transferred
5 to the next generation, even without exposure of second generation individuals to
6 maternal separation (van dem Wijngaard et al., 2013). Interestingly, fostering the
7 offspring of maternally deprived dams with dams that had not been exposed to
8 maternal separation prevented the development of hypersensitivity (van dem
9 Wijngaard et al., 2013).

24 Stress in adulthood has also been shown to lead to visceral hypersensitivity, including
25 the bladder. In a recent study (Lee et al, 2015) 10 days of 1h water avoidance stress in
26 anxiety-prone rats induced bladder hyperalgesia (increased visceromotor response to
27 instilling cold saline or rapid inflation of the bladder) and suprapubic hyperalgesia (an
28 index of referred bladder pain in rat). These effects were still evident months later,
29 after cessation of the stress.

40 Changes in the characteristics of the prefrontal cortex-PAG descending control
41 system may contribute to the long-term effect of early life stress in animals. Increased
42 responsiveness of the PAG to electrical stimulation has been reported in adult rats that
43 had been subjected to early life separation stress, suggesting that the circuitry in this
44 region had become hyper-excitable (Quintino-dos-Santos et al., 2014). Imaging using
45 PET in maternally separated rats, which developed stress-induced hyperalgesia in
46 adulthood revealed activation in the PAG in response to colorectal distension
47 (Wouters et al., 2012). After exposure to water avoidance stress, in addition to the
48 PAG, colorectal distension evoked significant deactivation of the frontal cortex

(Wouters et al., 2012), perhaps reflecting a stress-induced disinhibition of tonic forebrain influence on the descending pain control system in the PAG.

Exactly how exposure to chronic stress predisposes to development of visceral pathology and pain states is not clear. However, a number of studies have now shown that epigenetic mechanisms can contribute to the symptomatology of stress-evoked visceral hyperalgesia. Epigenetics refers to processes that lead to stable and/or heritable changes in gene function without alterations of the primary DNA sequence. Chronic social stress in rats increases DNA methylation and histone acetylation of genes that regulate visceral pain sensation in the peripheral nervous system. In rats in which hypersensitivity to colonic distension had been induced by exposure to repeated water avoidance stress, expression of the gene encoding the glucocorticoid receptor and cannabinoid CB1 receptors was reduced but expression of TRPV1 receptor increased in lumbo-sacral dorsal root ganglia (Hong et al, 2015). Within the brain reduced expression of the glucocorticoid receptor gene, with a concomitant increase in CRF expression, was also reported in amygdala (Tran et al., 2013).

CRF was first characterized as the hypothalamic neurohormone released in response to stressors in order to initiate the endocrine limb of the stress response. However, it also acts as a brain neurotransmitter that is released from neurons in limbic brain regions to mediate behavioral responses to stress. Interestingly, CRF is expressed in neurons of Barrington's nucleus (pontine micturition centre), which project to the spinal cord. These cells also collateralise to locus coeruleus, which is involved in arousal mechanisms (Valentino et al, 1996). Activation of spinally projecting CRF-containing neurons inhibits micturition and promotes urinary retention (Valentino et al, 2013). It has been suggested that prolonged retention may lead to the development

of bladder pathology and that afferent signals from the damaged bladder feed forward via locus coeruleus and Barrington's nucleus to further contribute to bladder dysfunction and a stressed phenotype. It will be of interest to discover whether epigenetic mechanisms in Barrington's nucleus contribute to these long-term changes.

Conclusion

The urinary bladder is a remarkable organ that is subject to a very sophisticated level of central nervous control that is influenced by emotional and psychosocial factors, which can produce surprisingly long-lasting effects. Recent findings provide a glimpse of the powerful influence not only of long-term stress but also the effect of early environment on visceral pain processing circuitry in adulthood. It is becoming clear that stress-induced visceral pain and its psychiatric comorbidities have a multifaceted etiology in which dysregulation of the hypothalamic-adrenal axis via inadequate or excessive activation, may contribute to the development of wide array of pathologies. An in depth understanding of neurophysiological mechanism which mediates voiding reflexes, including their modulation by emotional states and the factors which can give rise to pain from the urinary tract is essential to fully understand bladder function in health and will inform the development of new therapeutic strategies to treat conditions of dysfunctional bladder.

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Fig 1. Concept of 'cognitive voiding'. Afferent input from the bladder is subject to a high level of analysis based on context and social situation before the command to void is issued. Reproduced from Gillespie (2013) with permission.

Fig 2 Circuitry for micturition. The basic spino-midbrain-spinal circuit (purple arrows) is normally inhibited by tonic activity in a midbrain-thalamo-cortical loop (red arrows), which must be disinhibited to allow a void to occur. Under conditions of extreme urgency the anterior cingulate area may be stimulated to activate an emergency pathway, which bypasses the midbrain (yellow arrows). Depending on emotional state, activity in hypothalamic circuits (blue arrows) may further modulate the excitability of the midbrain circuit.

Abbreviations: dACC: dorsal anterior cingulate; Hip: hippocampus; Hyp: hypothalamus; INS: insula; PAG: periaqueductal gray matter; med PFC, lat PFC: medial and lateral prefrontal cortex; PMC: pontine micturition centre; SMA: supplementary motor area. Reproduced from the Griffiths and Fowler (2013) with permission.

Fig 3. Continuous cystometry in response to infusion of saline into the bladder (6ml h⁻¹) in a male adult urethane-anaesthetised rat. As the EEG cycles from an activated (low amplitude high frequency activity, low 0.5-1.5Hz band power) to a de-activated state (high amplitude, low frequency EEG waveform, high 0.5-1.5Hz band power) voiding threshold increases (red broken lines) and end-filling compliance decreases (increase in slope of red oblique lines). Crook and Lovick unpublished work.



Figure

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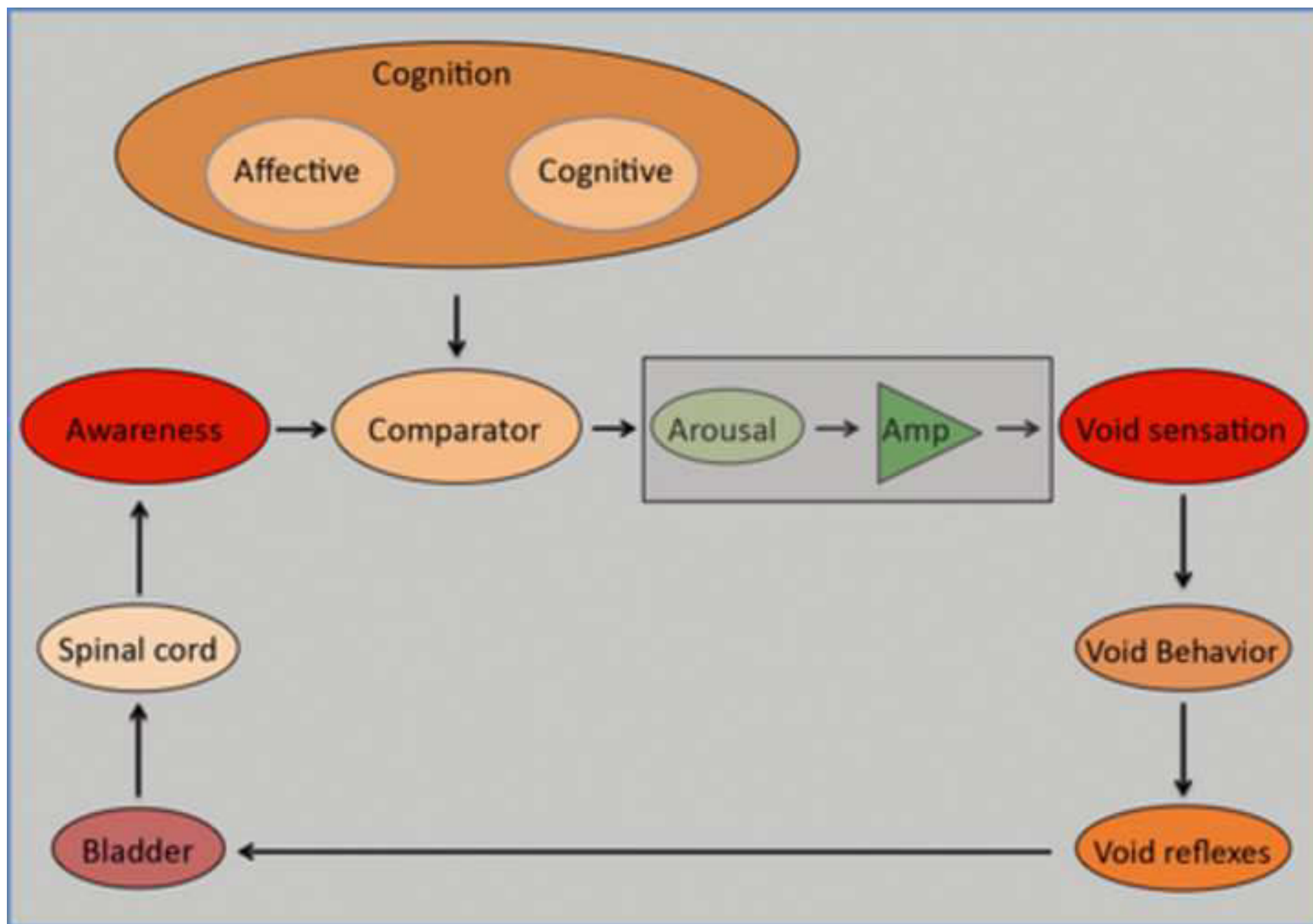
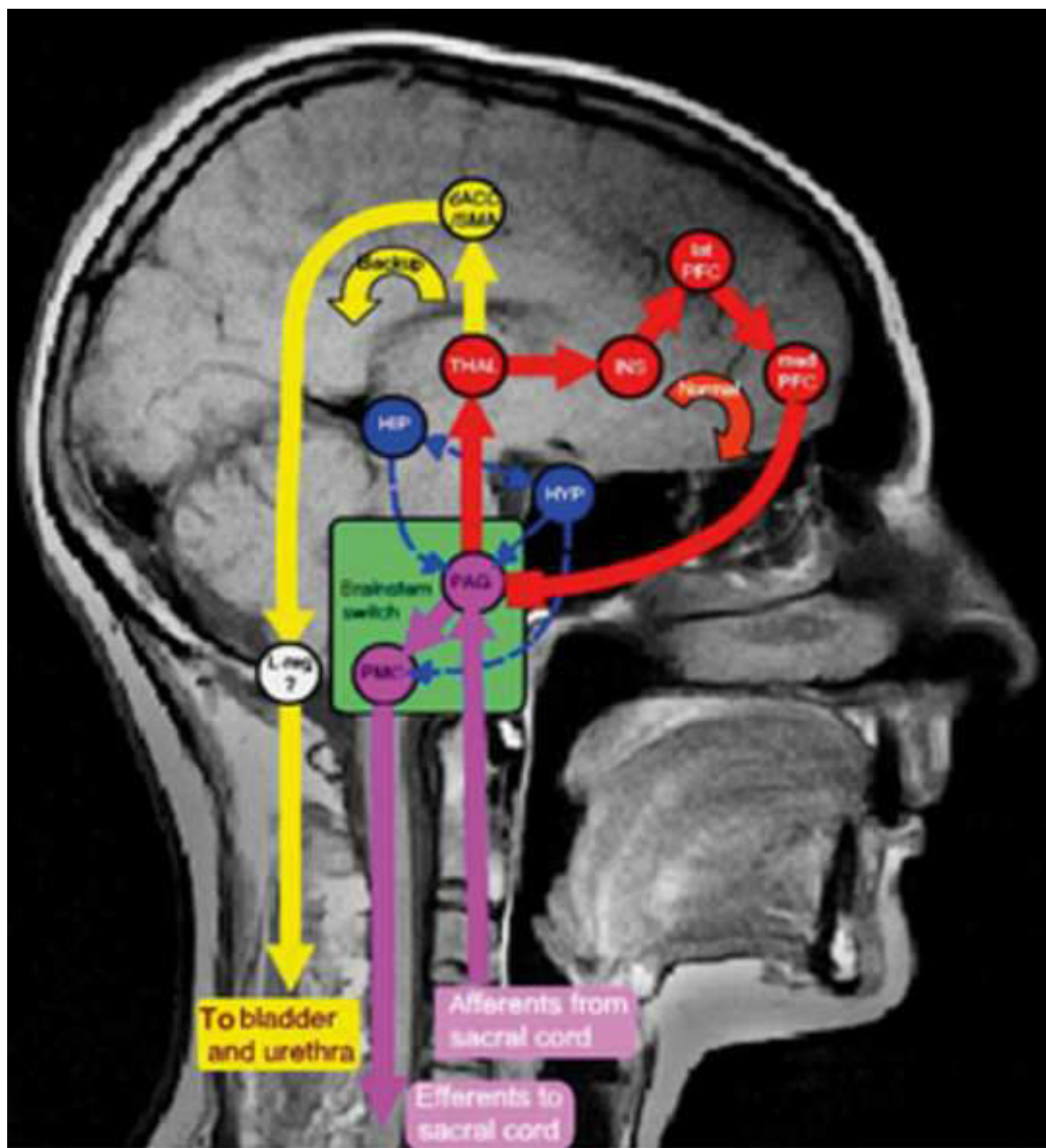
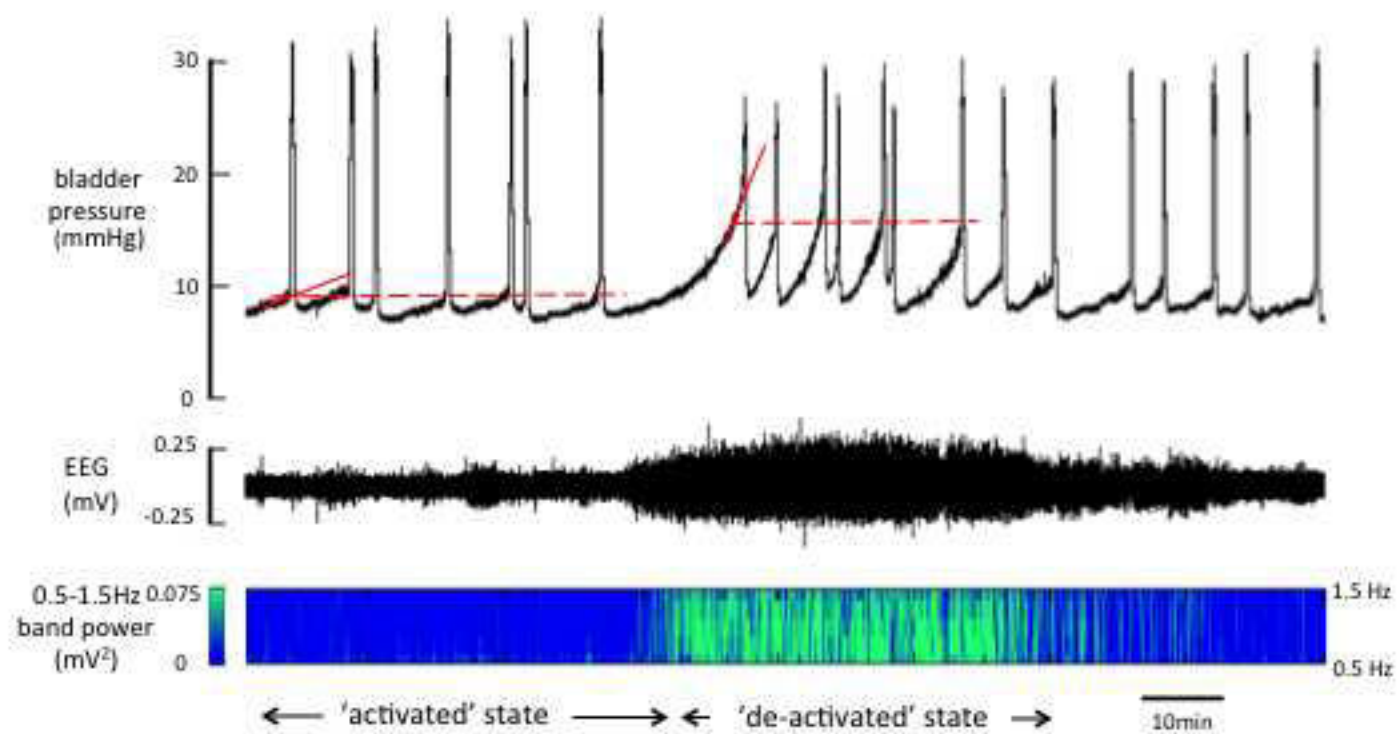


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